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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,787	01/10/2002	Chong-Sheng Yuan	466992000221	9117

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EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 01/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/043,787	YUAN, CHONG-SHENG	
	Examiner	Art Unit	
	Iqbal Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6-9,13,18,19,23,24,28-31 and 52-56* is/are pending in the application.

4a) Of the above claim(s) *36-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6-9,13,18,19,23,24,28-31 and 52-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Claims 1, 4, 6-9, 13, 18, 19, 23-24, 28-31 and 36-56 are pending.

In response to a previous Office action, a non-final requirement (mailed on August 8, 2005), Applicants filed a response and amendment received on November 8, 2005. Applicant's amendment of claims 1 and 6, canceling claim 51 and withdrawing claims 36-50 has been entered. Thus, Claims 1, 4, 6-9, 13, 18, 19, 23-24, 28-31 and 52-56 are pending in the instant Office action. Thus, Claims 1, 4, 6-9, 13, 18, 19, 23-24, 28-31 and 52-56 will be examined herein.

Withdrawn - Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Previous rejection of claims 1, 4, 8-9, 13, 18-19, 23-24, and 28-31 under 35 U.S.C. ə 112, second paragraph, as being indefinite with the recitation "a method of assaying Hcy, SAH or adenosine -----mutant SAH hydrolases encoded by nucleic acids having specifically recited GenBank accession numbers" is withdrawn by virtue of Applicant's amendment of claim 1.

Maintained - Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Previous rejection of claims 1, 4, 6, 8-9, 13, 18-19, 23-24, 28-31 and 52-56 under 35

U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. This rejection has been discussed at length in the previous office action mailed on August 8, 2005. It is maintained for the reasons of record and discussed below.

With respect to the claims 1, 4, 8-9, 18-19, 23-24, 28-31, and 52-56 the applicants argue that claim 1 has been amended to recite mouse (L32836), a rat (M15185), and two human (M61831 and M61832) nucleotide sequences which encode full length SAH hydrolase and the examiner acknowledge the Exhibit 2, where an alignment of human, rat and mouse SAH hydrolase encoded by the nucleotide sequences all have 430 amino acid residues and they are highly homologous. Applicants submit that amino acid sequence in SEQ ID NO: 1 is the same amino acid sequence encoded by nucleotide sequence having GenBank accession number M61831. Because of the high level of homology between these sequences, Applicants submit that the claims as amended are supported by structural features and by functional characteristics coupled with a known correlation between function and structure; and one skilled in the art can mutate any of these three genes to obtain mutant SAH hydrolase having binding affinity for Hcy, SAH or adenosine and having attenuated catalytic activity based on their homology to amino acid residues in SEQ ID NO: 1 that are directly interacting with the substrate and coenzyme.

Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 1, 4, 8-9, 18-19, 23-24, 28-31, and 52-56. The examiner acknowledges the amendment to the claim 1 and Exhibit 2 regarding alignment of human, rat and mouse SAH hydrolase encoded by the nucleotide sequences, where all the sequences have 430 amino acid residues and they are highly homologous but disagrees with the applicants contention that the claimed invention is adequately described. Claims 1, 4, 8-9, 18-19, 23-24, 28-

31, and 52-56 are directed to a method for assaying Hcy, SAH or adenosine in a sample with a genus of mutant SAH hydrolases encoded by nucleic acids having specific GenBank accession numbers, wherein said mutant SAH hydrolases have specific functions.

The genus of mutant polypeptides required to practice the claimed method is a very large genus with the potentiality of being a highly structurally variable genus. While the claim recites the polypeptides by SEQ ID NO: 185-188, which are defined by the corresponding amino acid sequences, this recitation is insufficient here as the polypeptides of SEQ ID NOS: 185-188 are not members of the genus of mutant SAH hydrolases recited. Recitation of the amino acid sequence of the protein being mutated does not provide support for structure of the modified product as the structure of SEQ ID NOS: 185-188 is being changed in an undescribed fashion. In the instant case there is no structural feature, which is representative of all the members of the mutant mammalian-derived SAH hydrolases recited in the claim. Many structurally unrelated mutant polypeptides are encompassed by the genus recited. The specification discloses only a few mutants of a single human placental SAH hydrolases which have the functional characteristics required, i.e. attenuated catalytic activity and binding affinity for Hcy, SAH or adenosine which is insufficient to adequately describe the required genus of mutant mammalian SAH hydrolases having these specific functional characteristics.

With respect to claims 6 and 52-56, applicants argue that claim 6 has been amended to recite that the human SAH hydrolase comprises the amino acid sequence set forth in SEQ ID NO: 1, which is the feature of claim 51, that is not rejected by the examiner and applicants submit that claims 6 and 52-56 as amended satisfy the written description requirement.

Applicant's arguments have been fully considered but are not deemed persuasive to

overcome the rejection of claims 6 and 52-56 as described above. The examiner acknowledges the amendment to the claim 6 and incorporation of SEQ ID NO: 1 but disagrees with the applicant's contention that the claimed invention is adequately described. Claims 6 and 52-56 are directed to a method for assaying Hcy, SAH or adenosine in a sample with a genus of mutant SAH hydrolases derived from human SAH hydrolases, wherein said mutant SAH hydrolase have specific functions.

The genus of mutant polypeptides required to practice the claimed method is a very large genus with the potentiality of being highly structurally variable genus. While claim 6 recites SEQ ID NO: 1, wherein the mutant mammalian SAH hydrolase is derived from said SEQ ID NO: 1, this recitation is insufficient here, as the polypeptide of SEQ ID NO NO: 1 is not member of the genus of mutant SAH hydrolases recited. Recitation of the amino acid sequence of the protein of SEQ ID NO: 1 does not provide support for structure of the modified product as the structure of SEQ ID NO: 1 is being changed in an undescribed fashion. In the instant case there is no structural feature, which is representative of all the members of the mutant mammalian-derived SAH hydrolases recited in the claim. The specification discloses only a few mutants of a single human placental SAH hydrolases, which is insufficient to adequately describe the required genus of mutant mammalian SAH hydrolases having these specific functional characteristics.

Claims 1, 4, 6, 8-9, 13, 18-19, 23-24, 28-31 and 52-56 remain rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method for assaying Hcy, SAH and adenosine with a mutant SAH hydrolase wherein said SAH hydrolase comprises SEQ ID NO: 1 or any of SEQ ID NOS: 185-188 and also specific substitutions at the positions recited in claim 7 or the corresponding positions of SEQ ID NOS: 185-188, and those positions

disclosed in the specification, wherein said mutant has the specific functional characteristics recited, does not provide enablement for a method for assaying Hcy, SAH, or adenosine with any mutant SAH hydrolase derived from SEQ ID NO: 1 or SEQ ID NOS: 185-188. This rejection has been discussed at length in the previous office action mailed on August 8, 2005. It is maintained for the reasons of record and discussed below.

With respect to the claims 1, 4, 6, 8-9, 18-19, 23-24, 28-31, and 52-56 the applicants notes that claim 1 has been amended to recite specific nucleotide sequences encoding the mouse, rat and human SAH hydrolases, and claim 6 has been amended to recite the human SAH hydrolase comprising the amino acid sequence set forth in SEQ ID NO: 1 and Exhibit 2, amino acid sequences are highly homologous between the mouse, rat and human SAH hydrolases recited in the claims. Applicants submit that one skilled in the art could apply the teachings of the specification to mutate these genes to obtain mutant SAH hydrolase having binding affinity for Hcy, SAH and adenosine but having attenuated catalytic activity based on their homology to amino acid residues in SEQ ID NO: 1 that are directly interacting with the substrate and coenzyme without undue experimentation.

Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 1, 4, 6, 8-9, 18-19, 23-24, 28-31, and 52-56. The examiner acknowledges the amendment to the claim 1 and Exhibit 2 regarding alignment of human, rat and mouse SAH hydrolase encoded by the nucleotide sequences, where all have 430 amino acid residues and they are highly homologous but disagrees with the applicants contention that the claimed invention is enabled for full scope claimed. Claims 1, 4, 6, 8-9, 18-19, 23-24, 28-31, and 52-56 are directed to a method for assaying Hcy, SAH or adenosine in a sample with a genus of

mutant SAH hydrolases encoded by nucleic acids having specific GenBank accession numbers, wherein said mutant SAH hydrolases have specific functions.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of mutant SAH hydrolases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of a few specific modifications of mutant SAH hydrolase.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any mutant SAH hydrolase having any number of modifications as defined in claim 7 because the specification does **not** establish: (A) regions of the protein structure which may be modified

without effecting mutant SAH hydrolase activity; (B) the general tolerance of mutant SAH hydrolase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any mutant SAH hydrolase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any polynucleotides encoding any mutant SAH hydrolase with an enormous number of amino acid modifications of the SAH hydrolase of SEQ ID NO: 1. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of mutant SAH hydrolase genes having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The rejection of claims 1, 4, 6, 8-9, 18-19, 23-24, 28-31, and 52-56 under 112 1st on written description and enablement could be overcome by incorporating the limitations of claim 7 in claims 1 and 6.

Withdraw- Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of

application for patent in the United States.

Previous rejection of claims 6 and 51 under 35 U.S.C. 102(b), as being anticipated by Yuan et al. is withdrawn by virtue of Applicant's amendment of claim 6 and explanation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 6 and 51-56 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6376210. This rejection has been discussed at length in the previous office action mailed on August 8, 2005. Due to the fact that no arguments have been presented traversing the Examiner's position and no terminal disclaimer has been filed, this rejection is maintained. Therefore, Claims 6 and 51-56 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6376210.

Applicants have requested to address this issue when other rejections are withdrawn.

Conclusion

Status of the claims:

Claims 1, 4, 6, 7, 8-9, 13, 18-19, 23-24, 28-31 and 52-56 are pending.

Claims 1, 4, 6, 8-9, 13, 18-19, 23-24, 28-31 and 52-56 are rejected.

Claim 7 is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

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